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Award Number: W81XWH-07-1-0720

TITLE: Inherited Retinal Degenerative Clinical Trial Network

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REPORT DATE: October 2013

TYPE OF REPORT: Final Addendum

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE October 2013		2. REPORT TYPE Final Addendum		3. DATES COVERED 30September2012-29September2013	
4. TITLE AND SUBTITLE Inherited Retinal Degenerative Clinical Trial Network				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-07-1-0720	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Patricia Zilliox Ph.D. email:pzilliox@fightblindness.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Foundation Fighting Blindness Clinical Research Institute Columbia, MD 21046				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The Foundation Fighting Blindness Clinical Research Institute (FFB CRI) (Formerly National Neurovision Research Institute (NNRI), the clinical arm of the FFB, established the National Eye Evaluation Research (NEER) Network, composed of a collaborative group of five clinical treatment and evaluation centers. The intent of this network was to advance the science of therapeutic and preventative interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research carried out encompassed: (i) a phase II clinical trial to evaluate the safety and efficiency of new therapeutic and preventive approaches, by repurposing an FDA-approved small molecule drug; (ii) natural history studies to develop standardized criteria to define disease stage, severity and progression; (iii) observational studies to enhance understanding of the natural history of these diseases for different genotypes and phenotypes; and (iv) evaluation of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions. The NEER Network also developed standard protocols for data collection maintained and expanded patient databases, classified by genotype and phenotype, which allowed for the timely identification of eligible patients and facilitate patient access for clinical participation and maintained readiness for collaboration with the Department of Defense, training program for military ophthalmologists in the latest technologies and diagnostic and treatment regimes.					
15. SUBJECT TERMS- Retinal Degeneration, Clinical Trial Network, non-invasive imaging treatment					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	21	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION:

The Foundation Fighting Blindness Clinical Research Institute (FFB CRI), the clinical arm of the Foundation Fighting Blindness (FFB), established the National Eye Evaluation Research (NEER) Network composed of a collaborative group of five Clinical Treatment and Evaluation Centers (CTECs) and a two support groups- the Clinical Coordinating Center and an independent visual image reading center. The intent of this Network remained the same throughout the award period as in the original application: to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research carried out encompassed:

- A Phase II clinical trial to evaluate the safety and efficacy of a new therapeutic and preventive approaches, by repurposing an FDA-approved small molecule drug
- Natural history studies to develop standardized criteria to define disease stage, severity and progression;
- Observational studies to enhance understanding of the natural history of these diseases for different genotypes and phenotypes; and
- Evaluation of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions.

The NEER Network devised standard protocols for data collection, maintained and expanded standardized patient databases, classified by patient genotype and phenotype, to allow for the timely identification of eligible patients and facilitate patient access for clinical trial participation. In addition, the NEER network maintained readiness to collaborate with the Department of Defense, training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens. An important reason for the development of the NEER network was that military populations mirror the civilian population, including for the incidence of retinal diseases. Soldiers and their families therefore suffer from the same sight-robbing retinal degenerative diseases as the general population. In addition, the military's expanding retiree population will suffer from age-related macular degeneration (AMD) and useful preventative or treatment regimen information will greatly enhance these persons lives by preventing them from losing vision.

The NEER network, in cooperation with COL Donald A. Gagliano, MD, MHA, DOD, Principal Advisor for Vision, Director, DODNA Vision Center of Excellence, and others in DOD, as appropriate, intended to develop a program to include military hospitals and ophthalmologists in clinical trials for Retinal Degenerative Diseases so that military personnel and their families will directly benefit from the new preventions, treatments and cures for these sight robbing diseases. Also, the NEER network planned to work with the appropriate military office to develop a fellowship and senior physician training and continuing education program for military ophthalmologists to obtain specialized training at NEER network academic centers in the latest technologies, including non-invasive imaging such as multifocal electroretinogram (mfERG), optical coherence tomography (OCT), and Adaptive Optic Scanning Laser Ophthalmoscopes (AOSLO). Unfortunately, despite ongoing readiness of the NEER network, circumstances necessitated that our DOD partners devote their time to other endeavors.

BODY:

The Foundation Fighting Blindness Clinical Research Institute (FFB CRI), the clinical arm of the Foundation Fighting Blindness (FFB), established the National Eye Evaluation Research (NEER) Network, which is composed of a collaborative core group of five (5) Clinical Treatment and Evaluation Centers (CTECs). The intent of the NEER Network was to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD). This was accomplished within the NEER Network through the conduct of clinical trials and other clinically relevant studies. Pertinent background information on the FFB, the FFB CRI, the retinal diseases to be studied, and the rationale underlying the need for and feasibility of this new Network are delineated below.

The Foundation Fighting Blindness is the world's largest source of non-governmental support for research on inherited orphan retinal degenerative diseases and dry AMD. Since its inception in 1971, the Foundation has raised more than \$500 million and, in the current fiscal year, is providing over \$21 million in funding for 138 grants, including Research Centers. The research projects of these grants are conducted by 190 research investigators at 73 Institutions, Eye Hospitals and Universities. In addition to funding researchers within the United States, FFB funding extends internationally including laboratories in Canada, England, France, Germany, Italy, Israel, China, and the Netherlands.

To promote collaborations between basic and clinical researchers and accelerate the advancement of promising preventive and therapeutic approaches to the clinic, the Foundation also supports Research Centers internationally. The Research Center Program involves inter-disciplinary groups of investigators conducting multiple research projects with an emphasis on translational research to facilitate clinical applications and the sharing of research tools, knowledge and data.

In 2003, the Foundation established the FFB CRI (formerly known as the National Neurovision Research Institute or NNRI), a non-profit entity, to capitalize on the fairly recent emergence of therapeutic and preventive products and devices that require rigorous clinical evaluation for safety and efficacy. The mission of the FFB CRI is to accelerate the translation of promising research on treatment and prevention approaches into clinical trials. On July 1, 2012, the FFB CRI was renamed from NNRI to the Foundation Fighting Blindness Clinical Research Institute (FFB CRI) in order to provide a better message that reinforces the link between FFB CRI and the Foundation Fighting Blindness.

Inherited orphan retinal degenerative diseases are a family of inherited pathologies with the ultimate consequence of photoreceptor death and severe visual impairment usually ending in blindness. In the United States, the total number of individuals affected by retinitis pigmentosa (RP) and other forms of rare inherited retinal degenerative diseases is estimated at approximately 200,000 individuals. RP, Stargardt disease, and Usher syndrome represent the predominant forms of inherited orphan retinal degenerative diseases and are estimated to affect ~80,000, ~100,000, ~25,000, and ~20,000 individuals in the U.S., respectively. Genetic heterogeneity is a key feature of each of these predominant diseases. To date, over 200 genes with mutations causing one or more forms of inherited orphan retinal degenerative diseases have been cloned, and over 50 more have been identified based on candidate gene studies or linkage mapping.

In the majority of inherited orphan retinal degenerative diseases, visual impairment is detected in the first or second decade of life. Assuming that 30% of individuals will reach legal blindness by their third decade of life, 30% by the fourth decade of life, 30% by the fifth decade of life, while 10% never reach legal blindness, and considering just the annual cost of blindness to the U.S. government, adjusted annually for inflation at a rate of 2.5%, then the cumulative minimal lifetime costs incurred by the U.S. government for the current civilian and military populations affected by inherited orphan retinal degenerative diseases is more than \$38 billion. This tremendous economic burden will not only continue to be incurred, but will increase unless efforts are made to define the molecular, biochemical and clinical parameters of these diseases and to advance capabilities to a point where rational, safe therapeutic strategies can be designed, tested and adopted as standard care.

While repeat evaluation and study of affected patients are vital to rigorously characterize the unique features of various diseases and the factors that cause disease progression, several obstacles in addition to the lack of research funding, often prevent the necessary frequency and thoroughness of patient examination. First, patients are often diagnosed by ophthalmologists who have limited training in the diagnosis and management of patients with rare forms of inherited orphan retinal degenerative diseases. Second, once patients are informed of the current lack of treatment options for their disease condition, they have little incentive for engaging in repeat clinical evaluations. Third, and perhaps more rare than the diseases themselves, is the number of clinicians fully trained in both the clinical and genetic aspects of inherited orphan retinal degenerative diseases. Training of additional clinical specialists in diagnostic and genetic evaluation of patients with rare forms of inherited retinal degenerative diseases has been identified as one of the most important resources needed to ensure that therapies for these diseases reach the clinic.

While inherited orphan retinal degenerative diseases account for a small portion of all vision loss, dry age-related macular degeneration accounts for approximately 90 percent of all age-related macular degeneration (AMD), affecting over 7 million individuals in the United States alone. With dry AMD yellow-white deposits composed of waste products from photoreceptor cells, called drusen, accumulate in the retinal pigment epithelium (RPE) tissue beneath the macula. The RPE tissue can lose its ability to process waste and drusen deposits accumulate in the RPE, reasons for this are being investigated with FFB support. These deposits are thought to interfere with the function of photoreceptors and the RPE in the macula, causing progressive degeneration of these cells with the eventual loss of vision.

Vision loss from dry AMD occurs very gradually over the course of many years. Central vision may even remain stable between annual eye examinations, and individuals with dry AMD do not usually experience a total loss of central vision. However, vision loss may make it difficult to perform tasks that require finely focused vision (e.g., driving or reading). Although there are extensive research efforts underway to identify treatments for dry AMD, at this time the only proven treatment for late-stage drug AMD is the Age-Related Eye Disease Study (AREDS) antioxidant supplement regimen, stopping smoking, and eating healthfully.

Through the research programs conducted with the support of the FFB and, more recently, through the FFB CRI, and the National Eye Institute of the National Institutes of Health (NIH), basic scientific discoveries have shown that selected nutritional factors, neuroprotective drugs, and gene therapies are safe and can prevent visual loss or restore visual function in preclinical animal models of

certain genetically defined forms of inherited orphan retinal degenerative disease and dry AMD. While AREDS antioxidant formulation is a widely accepted treatment, clinical trials of other potentially more effective treatments are imminent.

Recent progress in the classification of mutations for various inherited orphan retinal degeneration and dry AMD genotypes and the development of treatment possibilities raise the likelihood that potential treatments will be ready for evaluation in clinical trials in the near future. Unfortunately, there are considerable obstacles to the successful conduct of these clinical trials, including:

- Lack of resources for the design and conduct of effective and efficient clinical trials for inherited orphan retinal degenerative diseases and dry AMD;
- Limited number and wide geographic distribution of potentially eligible patients across the U.S., making follow up examinations at one clinical center financially and logistically problematic, if not unfeasible;
- Limited number of retinal specialists with expertise in these diseases;
- Use of diverse, non-uniform approaches to measuring disease severity, stage and progression; and
- Unresolved methodologic issues, such as determination of clinically meaningful, reliable and valid outcome measures.

The development of a clinical trials network has shown its efficacy in being an efficient and valuable approach to overcome these obstacles and to maximize the resources currently available (see report below on the ongoing VPA clinical trial in the NEER network for autosomal dominant retinitis pigmentosa, and the ProgSTAR studies for Stargardt disease). As new interventions become available for clinical evaluation, the creation of such a network will provide the infrastructure necessary to facilitate the initiation and conduct of properly designed clinical trials of investigational therapeutic and preventive approaches and devices in a timely manner. The development of a clinical trials network in inherited orphan retinal degenerations and dry AMD required the cooperation of an interdisciplinary team with clinical, genetic, and basic science expertise.

KEY RESEARCH ACCOMPLISHMENTS:

NOTE: In 2010, the FFB CRI worked with TATRC to apportion the two grants it has received (-0189 and -0720) into consistent expenses. Previously, it had been submitted and approved by TATRC that the -0189 grant would support the NEER infrastructure while the -0720 grant would support the actual clinical trial and natural history studies, including CTEC costs associated with these functions. This is the final report for grant -0720 and will mirror the Key Research Accomplishments and Reportable Outcomes of the -0189 grant in the support of the continuing overall operation of the NEER network.

Establishment of the NEER Network:

The NEER Network Steering Committee met 2 times during the grant time period (December 2009 and June 2011).

Meeting #1: The Steering Committee met to discuss the NEER Network Charter and operational procedures, including submission of proposed research, Conflict of Interest issues, Human Subject Protections issues, and financial procedures.

Meeting #2: The Steering Committee reviewed the UCSD CTEC/Dr. William Freeman's results for his natural history studies for dry age-related macular degeneration, with intent to use this data to design a natural history study for inherited orphan retinal degenerations. Dr. Freeman had been piloting a natural history study and collected data to a standardized protocol and data collection system that could be transferred to all of the CTECs. A final report from UCSD was submitted to FFB CRI and subsequently submitted to DOD as part of the 2011-2012 annual report.

NEER Clinical Trials:

NEER's clinical trials are not complete but continue to progress on an expanded schedule to ensure adequate recruitment of subjects and will continue to utilize the DOD -0189 grant funds.

In 2012-2013, the NEER network continued its first clinical trial (the Valproic acid Study) using the University of Utah CTEC as the nucleating Center for the trial and 5 recruitment sites to ensure adequate enrollment (study goal = 90 randomized)- the Retina Foundation of the Southwest, Dallas, TX; the University of Miami, Miami, FL; the University of Tennessee, Memphis, TN; the Oregon Health & Sciences University, Portland, OR; and the University of Michigan, Ann Arbor, MI. The EMMES Corporation is the NEER Clinical Coordinating Center and the Translational Clinical Trials Center (TCTC) at the Casey Eye Institute, Oregon Health and Science University (OHSU) as the independent image Reading Center for NEER clinical trials.

The Data Safety Monitoring Board (DSMB) Safety Committee for the VPA study met twice this past year (Fall 2012 and Spring 2013- see appendices for the DSMB summaries^{1,2}). These meetings were in addition to meetings in previous years (November 2010, September 2011, and April 2012) that have been reported in previous Annual Reports. At all of the meetings, the DSMB reviewed VPA study progress and did not note any safety issues of concern and recommended the continuation of the study.

The second and third large NEER clinical studies are also continuing; these projects are 2 almost identical natural history protocols examining the progression of Stargardt disease (ProgSTAR trial). The main difference between the two protocols is that one will examine retrospective data and the other will collect

data prospectively. The study will utilize the staff of the Wilmer Eye Institute CTEC at the Johns Hopkins University to lead these investigations; the Johns Hopkins University will also participate as a clinical site. The first subjects for these studies were enrolled in August 2013.

The EZ Width/EZ Area Endpoint Validation Study was started with a design meeting in April 2013. EZ Width/EZ Area is the measurement, using Optical Coherence Tomography (OCT) scans of the retina, of the distance between the edge of the advancing RP degeneration on either side of the fovea. This measurement approach, as developed by Dr. Birch (Retina Foundation of the Southwest) and his team, is robust in its repeatability and accuracy, and seems to be considerably better in its predictability than other more traditional measures such as ERG or Visual Field to detect changes in retinal deterioration. EZ Width could, in the future, be considered a primary clinical endpoint for clinical studies where the objective is to evaluate the treatment effect of compounds to slow/stop progression of disease in patients with Retina Pigmentosa.

EZ Width is attractive because it is based on OCT scans (Spectralis) which are easy to acquire and less involved than ERG or visual field testing. If this measurement is confirmed to be more sensitive than visual field testing, it would be a better predictor of therapeutic effect. Because EZ Width is sensitive and predictable, the validation of the measurement would allow the design of clinical studies with significantly fewer patients, less clinical testing and shorter time periods. Therefore, FFB CRI would be able to evaluate new treatments faster and with significantly lower costs. FFB CRI also anticipates that validation of the EZ Width measurement method will motivate companies to develop treatments in the area of RP, similar to what was seen with geographic atrophy AMD after Autofluorescence was accepted as an endpoint.

The FFB Registry (My Retina Tracker™): The mission of the FFB Registry is to enable people with inherited, degenerative orphan retinal diseases, their doctors and researchers to actively collaborate in the research process. This will be accomplished by:

- Patients sharing information about the history, progression and personal impact of their disease in a central registry database,
- Patients authorizing their doctors to share their diagnosis, and select current and future clinical information,
- Patients participating in research studies when they are identified by researchers as potentially good subjects for their studies and contacted through the FFB Registry.

Current Detailed Status of the Clinical Trials of the FFB CRI NEER Network:

- **VPA Study-** Recruitment of participants into this NEER VPA clinical trial for autosomal dominant retinitis pigmentosa continues at six sites- the CTEC site at University of Utah and five additional recruitment sites- the Retina Foundation of the Southwest, Dallas, TX; the University of Miami, Miami, FL; the University of Tennessee, Memphis, TN; the Oregon health & Sciences University, Portland, OR; and the University of Michigan, Ann Arbor, MI. The protocol tests whether repurposing an FDA approved drug (valproic acid) will demonstrate whether VPA slows the progression of retinal degeneration in individuals with autosomal dominant retinitis pigmentosa.
 - o One hundred and fifty-eight subjects have been screened, 69 subjects have been randomized, and 15 potential subjects are currently undergoing screening procedures.

- o The Central Reading Center has trained and certified all clinical site ophthalmic personnel on required study procedures; annual personnel recertification has been completed in a timely manner.
- o Existing web-based data collection systems that were implemented by the NEER Coordinating Center for the current clinical trial have been operating as anticipated and monitoring visits are ongoing.
- ProgSTAR Natural History Prospective and Retrospective protocols- FFB CRI is working with the Wilmer Eye Institute CTEC at the Johns Hopkins University (as the lead Principal Investigator) and eight additional premier inherited retinal disease research sites from 4 different countries to conduct research following 2 protocols for natural history studies of Stargardt disease (one prospective data collection protocol and one retrospective data collection protocol). Most of the clinical sites are currently working to receive IRB and HRPO approval of the conduct of the protocols at their sites. One site (University of Pennsylvania has received all approvals and has enrolled the first 4 subjects into ProgSTAR.

Specifically, the ProgSTAR sites and support organizations are:

Study Director and Principal Investigator

Hendrik P.N. Scholl, M.D., M.A.

The Dr. Frieda Derdeyn Bambas Professor of Ophthalmology

Wilmer Eye Institute

Johns Hopkins University School of Medicine

Study Site Locations

Greater Baltimore Medical Center

Janet S. Sunness, M.D.

Medical Director

Hoover Low Vision Rehabilitation Services

Greater Baltimore Medical Center

Hospital University of Pennsylvania

Artur Cideciyan, Ph.D.

Center for Hereditary Retinal Degenerations

Scheie Eye Institute

Retina Foundation of the Southwest

David G. Birch, Ph.D.

Retina Foundation of the Southwest

University of Utah

Paul S. Bernstein, M.D., Ph.D.

Moran Eye Center

University of Utah School of Medicine

Cole Eye Institute at Cleveland Clinic

Elias Traboulsi, M.D.

Centre de Recherche Institut de la Vision Paris

José-Alain Sahel, M.D.

Centre de Recherche Institut de la Vision Paris

UMR-S968 INSERM/UPMC/CHNO des Quinze-Vingts

Universitätsklinikum Tuebingen (Eberhard-Karls University Hospital)

Eberhart Zrenner, M.D.

Institute for Ophthalmic Research

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Moorfields Eye Hospital, NHS Foundation Trust
Michel Michaelides, M.D., F.R.C.Ophth.
UCL Institute of Ophthalmology

Clinical Data and Biostatistics Coordination
Sheila West, Ph.D.
El-Maghraby Professor of Preventive Ophthalmology
Dana Center for Preventive Ophthalmology
Wilmer Eye Institute

Independent Central Image Reading Center
Srinivas R. Sadda, M.D.,
Associate Professor of Ophthalmology
Director, Medical Retina Unit
Ophthalmic Imaging Unit, Doheny Image Reading Center
Doheny Eye Institute
Keck School of Medicine
University of Southern California

- EZ Width/EZ Area Endpoint Validation Study- EZ Width/EZ Area is measured using Optical Coherence Tomography (OCT) scans of the retina, and measuring the distance between the edge of the advancing RP degeneration on either side of the fovea. This study utilized clinical data collected from the VPA study (described above) and:
 - o Evaluated the reliability of EZ area measurements in eyes with Retinitis Pigmentosa, and
 - o Evaluated the correlation of the EZ area with Visual Field changes (current accepted endpoint)

Analysis of the EZ Width validation data is currently ongoing and a meeting to discuss the results of the study has been scheduled for September 23, 2013.

- FFB Registry (My Retina Tracker™)- IRB submissions have been approved by both WIRB and USAMRMC HRPO (US Army Human Research Protection Office). The registry website has been established and is working smoothly for sighted users.

Beta-testing of the registry by sight-impaired testers identified problems with the assistive reading software used to interact with websites (e.g. JAWS). FFB CRI has worked with PatientCrossroads, American Federation of the Blind, the assistive reading software manufacturers, and the FFB Development web page contractor, to resolve all remaining concerns. Refinements have been completed and the website has now been made available to FFB constituents. Administrator controls on the website have been enabled and FFB CRI has become conversant with site administration.

REPORTABLE OUTCOMES:

Manuscripts: None until the supported VPA, ProgSTAR and EZ Width studies are completed and all data analyzed

Abstracts: None

Presentations:

- ProgSTAR was presented at the University of Pennsylvania Vision Colloquium, University of Pennsylvania, Philadelphia, November 5, 2012
- ProgSTAR was presented twice at the Deutsche Ophthalmologische Gesellschaft (DOG) Meeting in Berlin
 - SA55-367 A state-of-the-art in SD-OCT: Retinal morphology relevant for retinal disease; Hendrik Scholl (Baltimore/USA)
 - SA72-483 Genetics of the visual cycle- consequences for supplementation and therapy Genetik des Vitamin A-Zyklus- Konsequenzen für Nahrungsergänzung und Therapie; Hendrik Scholl (Baltimore/USA)
- ProgSTAR was presented at the 2012 Retina Society Meeting: RET IRD 01 trial
- ProgSTAR was presented at the AAO meeting in Chicago, November 12, 2012
- ProgSTAR was presented at the Association for Vision and Ophthalmology (ARVO) in Seattle, WA, May 2013
- ProgSTAR was presented at the Retinal Gene Therapy Conference in Portland, OR May 2013
- ProgSTAR was presented at the VISIONS 2013 conference in Baltimore, July 2013

Patents and licenses applied for and/or issued: None

Degrees obtained that are supported by this award: None

Development of cell lines, tissue or serum repositories: None

Informatics and Databases: In development for the ProgSTAR study and VPA study (used VPA study data for EZ Width study)

Animal Models: None

Funding applied for based on work supported by this award: None

Employment or research opportunities applied for and/or received based on experience/training supported by this award: None

CONCLUSION:

All CTECs continue to be available for NEER participation and have completed their NEER/FFB CRI establishment contracts. In addition, the FFB CRI has fully implemented infrastructure for the network (EMMES as the NEER Network Clinical Coordinating Center [NNCCC], the Translational Clinical Trials Center (TCTC) at the Casey Eye Institute, Oregon Health and Science University (OHSU) as the independent image Reading Center, and WIRB as the IRB of record for the NEER Network. FFBCRI has also continued to convene working groups of clinicians to define clinical trial parameters for inclusion/exclusion and endpoints for clinical trials in inherited retinal degenerations which are expected to be implemented in the NEER Network.

The FFB CRI/NEER, plans a meeting with the FDA to review the validation data for the proposed new retinal degenerations measurement endpoint: EZ width/EZ area. The continuation of the three NEER network clinical trials will continue under grant - 0189. The FFB CRI continues to work with both academic investigators and biotech companies on very promising leads for potential additional opportunities for the NEER network. It is anticipated that during the upcoming year, all of the NEER network active clinical trials will complete enrollment (one clinical and two natural history protocols) and follow-up study visits will be ongoing.

REFERENCES: NA

APPENDICES:

DSMB Fall 2012 and Spring 2013 meeting summaries attached (pages 11-18).

CONFIDENTIAL MINUTES
FFBCRI Data and Safety Monitoring Board Meeting
VP1 Study
Wednesday, October 10, 2012
10:30 AM – 2:00 PM ET

OPEN SESSION WITH ACTION ITEMS AND RECOMMENDATIONS

List of Attendees:

Data and Safety Monitoring Board (DSMB)	Stuart Fine, MD, Chair Gary Ingenito, MD, PhD Jacque Duncan, MD Dean Bok, PhD Marie Diener-West, PhD Karen Rothenberg, JD
FFBCRI	Stephen Rose, PhD Patricia Zilliox, PharmD, PhD Judith Chiostrì, MS
Clinical Coordinating Center (CCC)	Robert Lindblad, MD Paul VanVeldhuisen, PhD Aimee Wahle, MS

The meeting opened and ended with closed sessions of the DSMB. Minutes of the closed sessions are provided in a separate document accessible only to DSMB members and unmasked CCC study personnel. Below is a list of action items and recommendations based on discussions in both the open and the closed sessions, followed by the meeting minutes of the open session.

Recommendations:

1. The DSMB recommended the continuation of the VP1 study.
2. The DSMB did not identify any safety concerns in its review of the VP1 study report and does not have any recommendations for changes to the protocol.
3. The DSMB recommended sites focus on recruitment of participants with class II rhodopsin mutations (RHO) because those participants are most likely to respond to VPA.
4. The DSMB would like to have the quarterly recruitment report broken down by both site and mutation.
5. The DSMB recommended that the sample size not be reduced.
6. The DSMB encouraged FFBCRI to publicize the trial to constituencies most likely to have trial-eligible patients, including retina specialists, ophthalmologists, and optometrists. The DSMB also suggested increased communication with physicians at professional meetings such as ARVO and AAO.
7. The DSMB recommended that FFBCRI remind PIs of the need to inform participants when liver function tests and other lab values are abnormal, including the option for the participant to discontinue taking study medication and/or withdraw from the study.
8. The DSMB encouraged FFBCRI to track the extent to which the availability of travel reimbursement improves enrollment.

Action Items:

1. FFBCRI will communicate with the sites about the need to prioritize screening and enrollment of participants with rhodopsin mutations. COMPLETED
2. FFBCRI to provide information on the genetic mutations in the genotyped patients that may be eligible to participate at the University of Miami. COMPLETED
3. The CCC will summarize recruitment information by site and genetic mutation in future quarterly reports. COMPLETED

4. FFBCRI and the CCC will track the extent to which the availability of travel reimbursement reduces the rate of enrollment failure. COMPLETED
5. FFBCRI to provide information about the recruitment actions taken to date to meet study enrollment goals. COMPLETED
6. The CCC will follow-up with sites to inquire about discussions that have occurred with participants with elevated LFTs, and to ensure all sites are providing study participants with the option of discontinuing study drug and/or withdrawing from the trial for abnormal laboratory results. COMPLETED
7. The CCC will make the following modifications to data presentations in future DSMB reports:
 - a. Add distributional statistics, including interquartile range, to Closed Session Table 11 Summary of Study Medication Exposure and Overall Compliance. A graph may also be considered for presenting these data. COMPLETED
 - b. Provide summary tables and graphs of efficacy outcome data in the closed session report. COMPLETED
 - c. Modify adverse event (AE) summary tables that indicate the number of newly occurring AEs since the last DSMB meeting. COMPLETED
 - d. For tables presenting pre-screen and screen failures data, characterize RP patients who are ineligible due to the results of genetic testing as “autosomal dominant RP, not genetically characterized” rather than “not autosomal dominant for RP”. COMPLETED
8. FFBCRI and the CCC will provide the DSMB with updates about new publications on VPA and retinal degeneration. COMPLETED
9. The CCC will send out a clean version of the DSMB Charter to members and request member sign-off. COMPLETED
10. FFBCRI to schedule the next DSMB meeting to be a conference call on Thursday, April 4, 2013 from 1:30-3:30 pm ET. A face-to-face DSMB meeting will be scheduled on Wednesday, October 2, 2013 from 12:00-4:00 pm ET in Columbia, MD. COMPLETED

Open Session (Preliminary)

The Open Session began with Dr. Zilliox asking the DSMB to discuss several issues during the Closed Session. Dr. Zilliox expressed concern with study drug exposure in participants who require drug holidays or dose reductions due to elevated liver function tests (LFTs), and the impact of low study drug exposure on efficacy outcomes. Dr. Zilliox also requested that the DSMB discuss the population that would define the per protocol analyses, the possibility to conduct a futility analysis, and to consider stopping enrollment at 80 participants rather than the 90 participants noted in the protocol. These latter two requests originated from the FFBCRI Board. Dr. Zilliox stated that she has no safety concerns for the study.

The role of Steve Rose with the DSMB was discussed. Prior to the last meeting of the DSMB, which occurred on April 30, 2012, Dr. Rose informed the DSMB that he no longer was involved in the operational aspects of the VP1 study, and that FFBCRI would be transferring the role of Principal Investigator (PI) to Dr. Zilliox. With this knowledge, the DSMB approved Dr. Rose’s attendance during the closed session of the April 30th meeting. However, since that meeting, Dr. Rose was temporarily reinstated as the PI of the VP1 study to facilitate the process of activating the new clinical sites. The Department of Defense (DoD) required full IRB review to remove Steve Rose as study PI. FFBCRI did not want to delay activating the new sites while this administrative process was reviewed and approved by the DoD and IRBs, so Dr. Rose temporarily remained as the study PI. FFBCRI will soon submit to the DoD a request to transfer the role of PI from Dr. Rose to Dr. Zilliox for the VP1 study, and Dr. Rose will then be able to participate in the Closed Session of the DSMB again.

Open Session

Dr. Fine provided an overall summary of the major points of discussion during the initial Closed Session. He reported that the DSMB did not identify any safety concerns in the study. He discussed the issue of participants with dose reductions which may result in low VPA exposure, and stated that the therapeutic range is unknown for the VP1 study indication. Therefore, maintaining study participants on a lower dose to gather more information seems reasonable. Dr. Fine requested that further information be provided to the DSMB about the communication by the sites to participants with elevated liver function tests. The DSMB would like to know if participants were informed that they had elevated test results and about the option to discontinue the study medication/withdraw from the study.

Dr. Fine reported that the major concern of the DSMB is study recruitment. He offered suggestions from the DSMB about steps that could be taken to bolster enrollment, including publicizing the study through direct communications with retina specialists, ophthalmologists, optometrists, and to search local registries that may contain RP patients. The VP1 study could also be publicized at professional meetings such as ARVO and AAO. The DSMB also asked for clarification on how the four new sites were selected.

Dr. Fine stated that the DSMB recommends not to reduce the sample size from 90 to 80 participants. The primary reason is that VPA has only been shown to be effective in some types of RHO mutations and the VP1 study has enrolled approximately one third of its participants with mutations in genes other than RHO, which may dilute any potential treatment effect with VPA. The DSMB discussed whether the eligibility criteria should be restricted to study participants with RHO mutations, but determined that rather than a protocol modification, study investigators should primarily focus on screening and enrolling participants with RHO mutations first before enrolling participants with other autosomal dominant mutations. Dr. Zilliox agreed with not reducing the sample size, noting that this request for consideration of sample size reduction came directly from the FFBCRI board.

Ms. Chiostrì described the selection process for the four new sites. Recommendations for potential new sites were provided by the two existing sites, University of Utah (Utah) and Retina Foundation of the Southwest (RFSW), the Reading Center, and the FFBCRI board. As an example, Dr. Weleber from the Reading Center recommended the University of Tennessee (Tennessee) be considered due to a familial population with the RHO mutation in Tennessee and surrounding areas.

Dr. Fine inquired about how sites are reimbursed, and Ms. Chiostrì explained that sites are paid on a per-patient per-visit basis, as well as being provided some up-front funding for staff training.

Ms. Chiostrì described the recruitment potential from the new sites and the RP population they are being drawn from. She reported that Tennessee has one new participant scheduled for screening every week until after Thanksgiving. She also indicated that the University of Miami (Miami) has a large database with approximately 60 patients already genotyped as autosomal dominant. Also at Miami, eighty patients in the database required genetic testing, so FFBCRI paid for the testing and 40 of those patients were genetically characterized as autosomal dominant. The details of the specific genetic mutations, such as how many participants had RHO genetic mutations, have not been provided to FFBCRI. Miami recently experienced many layoffs, including the study coordinator, which has resulted in delays due to the training of new study staff. One participant has been randomized at Miami. The DSMB requested FFBCRI provide information on the specific mutations of the potential participants at Miami.

Ms. Chiostrì noted that Oregon Health & Sciences University (OHSU) has a mix of patients, some with genetic screening already conducted. OHSU has 18 RP patients who are genotyped as autosomal dominant. University of Michigan has a database of RP patients but many have not yet been genetically tested.

The DSMB discussed other potential sites for the study, including sites in areas with large RP populations, such as Boston, Philadelphia, and New York City. FFBCRI noted that sites in Boston and Philadelphia were considered, but potential investigators from these areas did not express interest in participating in the VP1 study. Dr. Fine noted that historically, NIH-supported eye studies have not enrolled well from sites in the New York City area. Dr. Zilliox stated that she believed the four new sites could complete the enrollment of 90 participants, but was unsure how much time would be needed. Dr. Rose noted that FFBCRI had looked into the FFB registry but it has not been useful in identifying potential study participants.

The DSMB discussed potential ways to increase enrollment, such as publicizing the VP1 trial through direct communications with retina specialists, ophthalmologists, and optometrists and also at professional meetings such as ARVO and AAO. Dr. Fine suggested having investigators send personal letters to other doctors in their area. Dr. Duncan mentioned the need to create “buzz” about the study using resources such as RP blogs, Facebook, and listservs. Dr. Fine noted that a face-to-face investigator meeting at ARVO could be beneficial. Ms. Chiostrì stated that an investigators meeting was held at the 2012 ARVO meeting, and future meetings at ophthalmic meetings will be strongly considered. Ms. Chiostrì also shared activities conducted by new investigators such as Dr. Iannaccone at Tennessee, who has already made presentations to local doctors about the VP1 study. A monthly VP1 newsletter is also distributed to study investigators. Dr. Zilliox offered to provide the DSMB with monthly summaries of recruitment activities.

Ms. Chiostrì presented a slide on the additional travel funds provided by FFBCRI to study participants. She reported that Utah and RFSW are contacting participants who previously declined participation in the study due to travel costs. The DSMB noted that it was of interest to track the extent to which the availability of travel reimbursement improves enrollment.

The DSMB discussed potential new methods for genetic testing that were not available when the study was planned, in particular, exome sequencing, which could help identify more patients with autosomal dominant mutations than the current genetic testing. Dr. Rose responded that exome sequencing to identify potential study participants could be considered, but

noted it would be a long process to implement. He preferred that FFBCRI concentrate on recruitment at the four new sites before considering other kinds of genetic testing.

Dr. Duncan recommended describing RP patients who are ineligible due to the results of genetic testing as “autosomal dominant RP, not genetically characterized” rather than “not autosomal dominant for RP”. Tables presenting pre-screen and screen failures will be modified accordingly in future DSMB reports.

The DSMB inquired about discussions that have occurred with study participants with elevated LFTs. The DSMB would like to know if the participants were informed about abnormal laboratory results, and to ensure all sites are providing the option to study participants with elevated LFTs to discontinue study drug and/or withdraw from the trial. The CCC will follow-up with the sites to determine the information provided to participants.

Dr. Fine requested updates be provided to the DSMB within future reports about new publications on VPA and retinal degeneration.

The next two DSMB meetings were scheduled. A conference call on Thursday, April 4, 2013 from 1:30-3:30 pm ET is planned, and a face-to-face DSMB meeting will be scheduled on Wednesday, October 2, 2013 from 12:00-4:00 pm ET in Columbia, MD.

FFBCRJ Data and Safety Monitoring Board Meeting
VPI Study
Wednesday, May 15, 2013
3:00 PM – 5:00 PM ET

OPEN SESSION WITH ACTION ITEMS AND RECOMMENDATIONS

List of Attendees:

Data and Safety Monitoring Board (DSMB)	Stuart Fine, MD, Chair Gary Ingenito, MD, PhD Jacque Duncan, MD Dean Bok, PhD Marie Diener-West, PhD Karen Rothenberg, JD
Foundation Fighting Blindness (FFB)	Stepheo Rose PhD
Foundation Fighting Blindness Clinical Research Institute (FFBCRI)	Patricia Ziliox, PharmD, PhD Judith Chiostrì, MS
Clinical Coordinating Center (CCC)	Robert Lindblad, MD Paul VanVeldhuisen, PhD Jennifer McCormack, MS Aimee Wahle, MS Janet Van Dyke

The meeting opened with an executive closed session of the DSMB. After the executive session, unmasked staff from the Clinical Coordinating Center and Foundation Fighting Blindness joined the DSMB for a brief closed session. The closed session was followed by an open session of the DSMB, and the meeting ended with another closed session. Minutes of the closed sessions are provided in a separate document accessible only to DSMB members and unmasked staff from the CCC and FFB.

Below is a list of recommendations and action items based on discussions in both the open and the closed sessions, followed by the meeting minutes of the open session.

Recommendations:

1. The DSMB recommended the continuation of the VPI study.
2. The DSMB recommends sites continue to focus on recruitment with efforts to complete enrollment of the trial by the next DSMB meeting on October 2, 2013.
3. The DSMB encourages randomization of participants with the RHO mutation because those participants may be most likely to respond to VPA based on previously-published literature.
4. The DSMB would like investigators to be aware of the May 6, 2013 FDA warning based on results from a recent study which reported that the use of valproate products in pregnant women can lead to decreased IQ scores in exposed children. The FDA recommended that valproate products no longer be used as a preventive measure against migraines in pregnant women. For the VPI study, investigators should continue to be cautious in enrolling females of childbearing potential and ensure that those participants use effective birth control.
5. The DSMB suggested a subgroup analysis of RHO participants to be examined at the next DSMB meeting. Note: subsequent to the DSMB meeting, this recommendation was not included in the list of recommendations to the sites based on communication between Dr. Fine and the CCC and that the DSMB, FFBCRI, and the CCC will discuss prior to the October 2013 DSMB meeting the implications and timing of the subgroup analysis before any subgroup analyses are performed.
6. The DSMB did not recommend a futility analysis at this time, but would consider having the CCC perform a futility analysis should recruitment be ongoing at its October 2013 meeting.

Action Items:

1. FFBCRI to provide the DSMB with a report summarizing recruitment by the end of August. UNDER DEVELOPMENT
2. The CCC will prepare the regular quarterly recruitment report by July 31, 2013. COMPLETED
3. In consultation with FFBCRI, the CCC will create a plan for a RHO subgroup analysis for review by the DSMB as part of the materials for the July quarterly report. If required, the CCC will perform the analysis for the October DSMB meeting based upon the DSMB's response. COMPLETED
4. A face-to-face DSMB meeting will occur on Wednesday, October 2, 2013 from 12:00-4:00 pm ET in Columbia, MD. SCHEDULED

Open Session

Dr. Zilliox reported on the recent Investigator Meeting in Dallas, TX on February 25, 2013. She stated that it was a successful meeting and believes there is a renewed commitment to complete enrollment in the VP1 study over the next few months. Dr. Zilliox explained that beyond determining the efficacy of VPA, the VP1 study also provides a unique opportunity to collect natural history data on RP patients. During the Investigator Meeting, the study investigators expressed that they were encouraged by this opportunity.

Dr. Zilliox noted that as of the date of the DSMB meeting on May 15, there were 59 participants randomized and 18 participants in active screening. In addition, approximately 30 additional potential participants have been identified by the sites. Together, these numbers indicate that reaching enrollment of 90 participants is plausible.

Dr. Zilliox reported that there was also a recent meeting to discuss the new clinical endpoint EZ width, and explained that data from the VP1 study can be used as a basis to validate this measure. Dr. Duncan provided a description of the ellipsoid zone (referred to as EZ) width measurement, which is the distance calculated from spectral domain OCT scans between the edge (i.e., the inner segment/outer segment) of the advancing RP degeneration on either side of the fovea. She stated that the EZ width is an objective structural measure that may correlate with the I4e isopter on Goldmann's visual field, and because it has less variability than functional measures of visual field, it could be an important outcome measure to predict progression of RP in clinical trials. Dr. Duncan noted that data from the VP1 study provides a unique opportunity to validate the EZ width measurement.

Dr. Zilliox stated that FFB is considering an ancillary follow-up study on VP1 study participants for three additional years post VPA treatment to allow continued collection of data on disease progression, including assessment of EZ width.

Ms. Chiostrì discussed efforts by FFBCRI to increase enrollment in the VP1 study. She reported an increase in screening and randomization since the Investigator Meeting in Dallas on February 25. FFBCRI has increased travel funds for participants and added flexibility for sites to provide financial assistance to participants (payments vs. reimbursements). FFBCRI has also provided sites with a service to assist in finding current contact information for potential participants who have can no longer be located, and two sites have found 10-12 potential participants using the service. Dr. Fine inquired about the status of University of Miami (Miami), because recruitment at this site appears to be lagging. Ms. Chiostrì noted that Miami has had good results using the service to find RP patients from their database who had moved. Ms. Chiostrì explained that Miami has experienced delays receiving genotype results from the Carver Lab in Iowa, which has impacted recruitment, so FFBCRI has paid to have the results expedited. Ms. Chiostrì stated that FFBCRI has received funding to create a registry of RP patients. Dr. Fine noted that it will be important for registry patients to be contacted several times a year so that patients are not lost.

Dr. Fine inquired about the timeline to complete recruitment. Ms. Chiostrì replied that the current goal is to complete enrollment by the end of July, but realistically this could extend into September or later. Dr. Zilliox believes that there are enough patients either in active screening or identified for screening to complete enrollment. Dr. Fine stated that it would be phenomenal if enrollment finished by the end of the year. Dr. Fine requested that FFBCRI send the DSMB a recruitment report by the end of August, and Ms. Chiostrì agreed to send this report.

Professor Rothenberg asked about the amendment to the protocol to allow enrollment of participants before genotyping has been completed, provided that the participant has a family member with a confirmed adRP mutation. It was explained that if a participant has a genetically-confirmed familial history of adRP, the participant has a high likelihood of also having genetically-confirmed adRP.

Dr. Zilliox requested that the DSMB consider during the closed session the FFBCRI Board's request to perform an interim analysis, even though she and Ms. Chiostrì do not favor performing a futility analysis at this time. (Note: see the recommendation section above for the results of the discussion on a futility analysis).

Ms. McCormack provided a description of data on treatment exposure and compliance included in Tables 16 and 17 and Figure 2. She noted that compliance calculated based on pill counts was generally good. Ms. McCormack also reported that there were six participants that terminated study drug early (Table 15). She explained that two of the early medication terminations stopped study drug after 52 weeks of exposure but prior to the Week 52 study visit due to expiration of the study drug.

The DSMB discussed the adverse events (AEs) reported so far in the VP1 study. Dr. Lindblad stated that he expected to see the AEs that have occurred from treatment with VPA. He noted that in general VPA has been fairly well tolerated by participants. Professor Rothenberg inquired about the two serious AEs (SAEs), which were both considered unrelated to study drug: arthritis in hip and cut hand. Dr. Lindblad reported that there were no pregnancies. Ms. McCormack noted that one participant in screening was found to be pregnant but was not randomized. She also reported that there has been one additional SAE since the database freeze, which was atrial fibrillation in a participant with a history of atrial fibrillation. This SAE was considered unrelated to study drug.

A face-to-face DSMB meeting is scheduled on Wednesday, October 2, 2013 from 12:00-4:00 pm ET in Columbia, MD.